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10/540,854	09/01/2006	Nicole Francine Rouquet	065691-0396	2346

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EXAMINER	
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1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,854	ROUQUET ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *10,11 and 13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 12 and 21-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Amendment to the Claims filed 1 February 2010 is received and entered. Applicant's Amendment to the Specification filed 4 November 2009 is received and entered. This US Application 10/540,854, filed 1 September 2006, is a National Stage Entry of PCT/FR2003/003897, filed 24 December 2003, which claims priority from French patent application FR 02/16785, filed 27 December 2002. Claims 21-22 are new. Claims 1-22 are pending. Claims 10-11 and 13-20 are withdrawn. Claims 1-9, 12 and 21-22 are under examination in this action.

Claims 10-11 and 13-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 24 April 2009.

All objections and rejections not repeated herein are withdrawn.

Response to Amendment

It is noted for clarity of the record that the claim amendment filed 1 February 2010 contains text in the term "its" in claims 13 (line 2) and claim 14 (line 2) that was previously deleted but is still present and showing a strike-through. In the interest of compact prosecution, and as this does not preclude examination, the examiner is interpreting the presence of the term "its" with a strike-through as an inadvertent error which was meant to have already been deleted.

Please note that the applicant is reminded that amendments to the claims filed on or after July 30, 2003 must comply with 37 CFR 1.121(c) which states:

(c) *Claims*. Amendments to a claim must be made by rewriting the entire claim with all changes (*e.g.*, additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

Claim Rejections - 35 USC § 103-maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 and 12 stand rejected and new claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Troczynsky et al in "Biofunctional Hydroxyapatite Coatings and Microspheres for In-Situ Drug Encapsulation" (WO 02/085330, published 31 October 2002; of record).

Applicants' arguments have been fully considered but are not found persuasive.

Currently amended Claim 1 is drawn to a method for attaching DNA in plasmid form to the surface of calcium phosphate ceramic or powder, comprising (a) hydrating of the calcium phosphate powder or calcium phosphate ceramic in a phosphate buffer solution not saturated with calcium and phosphate, (b) immersing the products obtained in step (a) in a phosphate buffer solution not saturated with calcium and phosphate containing a single- or double-stranded DNA for periods varying from a few minutes to several hours, and (c) producing calcium phosphate particles containing the DNA attached to an outer surface of the particles.

Troczynsky et al teach a hydration of the calcium phosphate powder or calcium phosphate ceramic in a phosphate buffer solution not saturated with calcium and phosphate (step a), stating: "The microspheres of the precursors can be exposed to a water-based solution of phosphate ions and incubated in a humid environment at a temperature of 20-50°C to promote dissolution of the precursors and precipitation of calcium phosphate phase" (e.g. paragraph bridging pages 10-11 and page 13, lines 1-5), and teach an immersion of the products obtained in step (a) in a phosphate buffer solution not saturated with calcium and phosphate containing a single- or double-stranded DNA for periods varying from a few minutes to several hours (step b) (e.g. page 13, lines 5-9) thus producing calcium phosphate particles containing DNA molecules

attached to the particles (step c) (e.g. page 13, lines 9-11) stating that: "[a] crystalline hydroxyapatite powder can be added to the precursors slurry to promote crystallization of hydroxyapatite calcium phosphate phase during the incubation period" and continue "[a] therapeutically active material can be added to the precursors slurry for encapsulation during crystallization of the hydroxyapatite calcium phosphate phase during the incubation period", further stating that "[t]he therapeutically active material can be a drug, a protein, a gene or DNA" (page 10, lines 21-26).

Currently amended Claim 3 depends from Claim 1 and specifies that the immersion is carried out for at least 1, 5, 10 or 30 minutes up to about 12, 24 or 48 hours at a temperature ranging from 15 to 50°C. Newly added Claim 21 depends from claim 3 and specifies that the immersion is carried out at about 37°C.

Regarding Claims 3 and 21, Troczynsky et al teach the process of making the calcium phosphate (in particular hydroxyapatite) microspheres (particles) designed specifically for gene therapy through gene/DNA/plasmid delivery occurs at room-temperature (i.e. about 25°C) and teach the drug material (e.g. DNA) is exposed to water-based solution of sodium phosphate and placed in an incubator at 37°C, 100% relative humidity, for up to 24 h. (e.g. page 12, lines 21-23).

Claim 4 depends from Claim 1 and specifies that the calcium phosphate particles are kept immersed in a culture medium of the cell culture media type. Claim 5 specifies within Claim 4 that the calcium phosphate particles are immersed for about a few minutes to a few days. Claim 6 specifies within Claim 4 that the calcium phosphate particles are immersed at a temperature ranging from 15 to 50°C, and newly added claim 22 depends from claim 6 and specifies that the

immersion is carried out at about 37°C. Claim 7 specifies within Claim 1 that step b) is carried out by means of a medium simulating extracellular fluids or a medium of the cell culture media type containing the nucleic acids, said medium being nondenaturing for the DNA and not saturated with calcium and phosphate; this medium causing epitaxial carbonated apatite growth at the surface of said powders and ceramics. Claim 9 depends from claim 7 and specifies that steps (b) and (c) occur under physiological pH conditions.

Regarding Claims 4-7, and 9, Troczynsky et al teach the production of calcium phosphate particles is carried out by means of a medium simulating the extracellular fluids or a medium of the cell culture media type (also called "simulated body fluid) containing the drug (i.e. DNA as disclosed as a gene therapy drug), said medium being nondenaturing for the DNA and not saturated with calcium and phosphate; this medium causing epitaxial carbonated apatite growth at the surface of said powders and ceramics (e.g. page 17, lines 8-12 and page 19, lines 9-11). Troczynsky et al teach the process of making the calcium phosphate (in particular hydroxyapatite) microspheres (particles) designed specifically for gene therapy through gene/DNA/plasmid delivery occurs at room-temperature (i.e. about 25°C) and teach the drug material (e.g. DNA) is exposed to water-based solution of sodium phosphate and placed in an incubator at 37°C, 100% relative humidity, for up to 24 h. (e.g. page 12, lines 21-23).

Claim 8 specifies within Claim 1 that steps (a) and (b) are carried out simultaneously or successively. Regarding Claim 8, Troczynsky et al teach that steps (a) and (b) are carried out simultaneously or successively (e.g. page 10, lines 21-26; page 12, lines 21-23; page 13, lines 1-11).

Claim 12 is drawn to a method of preparing a medicament for transfecting *in vivo* cells contained in a tissue or in an organ utilizing the particles obtained by the method as claimed in claim 1. Regarding Claim 12, Troczynsky et al teach therapeutic hydroxyapatite coated microspheres for the delivery of DNA to cells *in vivo*, contained within an organism (e.g. contained in a tissue or in an organ) (e.g. see abstract, lines 1-11 and page 6, lines 27-30).

Claim 2 depends from Claim 1 and specifies that the solution in step (a) and (b) comprises a 0.12 M phosphate buffer (pH 6.8).

Troczynsky et al differs from the instant invention because although they teach a phosphate buffer solution that is 0.25 M (page 16, lines 18-19 and page 18, lines 32-35) and a PBS solution that is pH 7.4 (page 17, Example 4, line 31) they fail to explicitly teach that a phosphate buffer solution of steps (a) and (b) comprises a 0.12 M phosphate buffer (pH 6.8) (e.g. instant Claim 2).

In addition, Troczynsky et al **fails to** explicitly teach that the type of DNA is plasmid DNA or that the DNA is explicitly attached to the particle "outer surface".

In the instant case, it would have been *primafacie* obvious to one of ordinary skill in the art at the time the invention was made to use plasmid DNA for the DNA attached to the particles to be plasmid DNA because plasmid DNA is the DNA form most often used for gene therapy and DNA transfection methods and is the form most often prepared in large preparations in the laboratory.

In addition, it would be *primafacie* obvious for the DNA to be attached to the particle outer surface since the attachment of the DNA would inherently occur on a particle surface.

In addition, absent evidence to the contrary, it would have been *primafacie* obvious to use a phosphate buffer solution comprising a 0.12 M phosphate buffer (pH 6.8) in combination with the method of Troczynsky et al because et al because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. One would have a reasonable expectation of success combining the teachings of the art because Troczynsky et al state that "we disclose hereby a new, safe and inexpensive way to deliver drugs, proteins, genes and antisense oligos in vivo" (page 7, lines 19-20) and the use of a phosphate buffer solution that is 0.12 M (pH 6.8) for the purposes of solutions containing DNA was routinely practiced at the time of the invention.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result when utilizing a phosphate buffer solution that is 0.12 M (pH 6.8) in the method of Troczynsky et al.

Applicants' response is to traverse. Applicants' arguments have been fully considered but are not found persuasive. Applicants have amended claim 1 to recite "an outer surface of the particles" in order to further distinguish WO 02-085330. Applicant argues that:

> WO 02-085330could not render obvious the omitted feature of attachment at an outer surface, because this reference relates exclusively to encapsulating various substances, including DNA, inside a layer of calcium phosphate material.

Applicants' continue that:

> WO 02-085330 discloses "encapsulation, and subsequent controlled release" of therapeutically active agents from "coatings and microspheres" (Abstract, lines 7-8). WO 02-085330 states (page 1, lines 4-6, and page 13, lines 13-14; emphases added):
>
> > This invention relates to novel room-temperature process for obtaining calcium phosphate, in particular hydroxyapatite, microspheres and coatings with

> encapsulated drugs, proteins, genes, DNA for therapeutical use.
> As a result of this protocol, a 10-1000 μm large, nano-to-submicron porous CPC-HA microspheres matrix encapsulating the drug material is achieved.

Applicants continue:

> This reference nowhere discloses attachment of a pharmaceutically active agent to an outer surface of particles. Indeed, the encapsulation disclosed in WO 02-085330 could at most be interpreted as yielding some form of attachment at an inner surface of a particle.

In addition, Applicants note "the following further distinctions over WO 02-085330 to support patentability".

> The present invention is aimed at a process allowing the attachment of DNA molecules in plasmid form to the surface of ceramic particles. In other words, the particles according to the invention are treated by fritting at high temperature, whereas WO 02/085330 particles are obtained by precipitation. Thus, Applicants conclude that as a result, "D1 particles are formed as a network of crystals not linked by joints and thus are less dense and stable". In addition, Applicants submit that "particles obtained by precipitation are more soluble compared to ceramic particles", and state that thus, as a consequence, "particles of WO 02/085330 encapsulates DNA but it is difficult to foresee what this encapsulation does to the integrity and functionality of DNA molecules".
>
> This is not a pitfall encountered in the particles according to the present invention since DNA molecules cannot be encapsulated in ceramic. They are attached to the surface of the particles and attachment prevents degradation in cell organs having low pH as well as by nucleases of the cell cytoplasm.
>
> Another advantage of the present invention is to allow liberation of the DNA molecules when the pH of the environment changes, which liberation is not possible in particles encapsulating the DNA like WO 02/085330 particles.

In summary, Applicants submit that "WO 02-085330 would not lead a skilled artisan to attach plasmid DNA to an outer surface of particles as defined in the present claims".

Applicants' arguments have been fully considered but are respectfully not found persuasive. Although Applicants' arguments are well-taken, the arguments are not persuasive because the applicant's arguments are not commensurate with the scope of the claims, as written. Although the claims are interpreted in light of the specification, limitations from the specification

are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). For instance, Applicants' argument that "the particles according to the invention are treated by fritting at high temperature, whereas WO 02/085330 particles are obtained by precipitation" is not commensurate with the scope of the instant claims as they do not require "fritting at high temperature" and since the claim language uses the open claim language "comprising" the claims, as written, do not exclude precipitation. In addition, Applicants arguments regarding the peculiar benefits of ceramics are also not commensurate with the scope of the claims, as written, as the claims do not require ceramic but are drawn to a method for attaching DNA in plasmid form to the surface of calcium phosphate powder or calcium phosphate ceramic using either calcium phosphate powder or calcium phosphate ceramic.

In addition, Applicants' arguments are not persuasive because Troczynsky et al teach the production of calcium phosphate particles is carried out by means of a medium simulating the extracellular fluids or a medium of the cell culture media type (also called "simulated body fluid) containing the drug (i.e. DNA as disclosed as a gene therapy drug), said medium being nondenaturing for the DNA and not saturated with calcium and phosphate; this medium causing epitaxial carbonated apatite growth at the surface of said powders and ceramics (e.g. page 17, lines 8-12 and page 19, lines 9-11). Troczynsky et al teach the process of making the calcium phosphate (in particular hydroxyapatite) microspheres (particles) designed specifically for gene therapy through gene/DNA/plasmid delivery occurs at room-temperature (i.e. about 25°C) and teach the drug material (e.g. DNA) is exposed to water-based solution of sodium phosphate and placed in an incubator at 37°C, 100% relative humidity, for up to 24 h. (e.g. page 12, lines 21-23), and therefore, WO 02-085330 would lead a skilled artisan with a reasonable expectation of

success to produce calcium phosphate particles containing DNA molecules attached to an outer surface of the particles.

In view of the foregoing, the method of claims 1-9, 12, 21-22, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a)*.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
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